orphanet

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Procedural document: data collection and registration of clinical trials

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I. Introduction

1. Purpose/objectives

Orphanet offers, amongst a range of expert resources on rare diseases, a directory of national and multinational clinical trials aiming to help:

- clinical investigators working in the field of rare diseases find each other, establish collaborations, recruit patients;
- patients and general public retrieve information on ongoing clinical trials for a particular disease, and stay informed on clinical trials that are recruiting;
- experts, funding agencies and pharmaceutical industry obtain visibility on therapeutic development in the field of rare disease.

This document aims to explain the set of criteria used, and the workflow of the collection, registration and update of national and multinational clinical trials on rare diseases.

2. Disclaimer

- This procedural document is part of the OrphaNetWork Direct Grant (831390), which has received funding from the European Union's Health Programme (2014-2020).

- The content of this procedural document represents the views of the author only and is his/her sole responsibility; it can not be considered to reflect the views of the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.

3. Range of application

The present procedure applies to all the clinical trials and the networks of clinical trials registered in Orphanet. The registration and update of the clinical trials is performed by the Orphanet national teams (ONT) having signed a Network Agreement and a Data Transfer Agreement (DTA) with the Orphanet Coordinating Team (OCT).

4. References

- Orphanet Standard Operating Procedures
- **Clinical trials.gov:** A web-based resource that provides the public with access to information on publicly and privately supported clinical studies, in human volunteers, conducted around the world. Clinical trials.gov is supported by the American National Institutes of Health.
- **European Union Drug Regulating Authorities Clinical Trials (EudraCT):** European Clinical Trials Database of all interventional clinical trials of medicinal products commencing in the European Union from 1 May 2004 onwards.
- **International Clinical Trials Registry Platform (ICTRP):** A platform supported by the

World Health Organization, that provides access to a central database containing the trial registration data sets provided by other national and international registries as well as links to the full original records.

- **International Rare Diseases Research Consortium (IRDiRC):** Consortium that unites national and international governmental and non-profit funding bodies, companies (including pharmaceutical and biotech enterprises), umbrella patient advocacy organisations, and scientific researchers to promote international collaboration and advance rare diseases research worldwide.https://irdirc.org
- **World Health Organization (WHO):** a specialised agency of the United Nations responsible for international public health.

5. Definitions

Clinical study: A research study using human subjects to evaluate biomedical or health-related outcomes. There are two types of clinical studies: interventional studies (or clinical trials) and observational studies[1].

Clinical trial (or interventional study): A clinical study in which participants are assigned to receive one or more interventions (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study protocol[2.] In Orphanet, interventions in clinical trials are limited to medicinal products and medical device assessments in the treatment or prevention of a rare disease or a group of rare diseases, conducted in at least one country of the Orphanet network or funded by an IRDiRC member.

Coordinator of multinational clinical trial: An investigator assigned the responsibility for the coordination of investigators at different centers participating in a multinational clinical trial. He/she should sign the protocol along with the sponsor.

Data transfer agreement (DTA): Contract between the providing and recipient institutions that governs the legal obligations and restrictions, as well as compliance with applicable laws and regulations, related to the transfer of such data between the parties.

Drug (medicinal product or medicine): A substance or combination of substances intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action [3].

EudraCT Number: Each trial registered in EudraCT database is issued with a unique EudraCT number, which identifies the protocol and trial throughout its lifespan.

European Reference Networks (ERNs): Virtual networks involving healthcare providers across Europe that aim to tackle complex or rare diseases and conditions that require highly specialised

[1] https://clinicaltrials.gov/ct2/about-studies/glossary
[2] *ibid*
[3] https://www.ema.europa.eu/en/about-us/about-website/glossary

treatment and a concentration of knowledge and resources[4].

Funding body: Organisation that provides funds to fulfill a specific and predetermined purpose (to perform a clinical trial, to develop a patient registry, etc.) to be carried out by the beneficiary(ies) of the financial support.

Geographical coverage: It describes the geographical coverage of a clinical trial. It can be national, European or global

Information scientist (IS): Member of the Orphanet team with a scientific and/or medical background in charge of collecting, producing and updating information provided in the Orphanet database.

Investigator: A doctor or a person following a profession agreed in the corresponding country for investigations because of the scientific background and the experience in patient care it requires. The investigator is responsible for the conduct of a clinical trial at a trial site[5].

Marketing authorization (MA): Refers to the approval for a medicine to be marketed. MA are granted only when a competent authority (or 'regulatory authority') has conducted a scientific evaluation, and is satisfied that a medicine is sufficiently safe and effective, and of high enough quality.[6]

Medical device: Any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;
- investigation, replacement or modification of the anatomy or of a physiological process;
- control of conception;

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.[7]

Multicentre Trial: A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator (it could be national or multinational).

Multinational clinical trial: A clinical trial that involves recruiting centres in multiple countries.

National clinical trial: A clinical trial that involves recruiting centre(s) in only one country.

[4] European Reference Network handout, ISBN 978-92-79-65469-5

[5] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

[6] https://www.eupati.eu/glossary/marketing-authorisation/

[7] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:01993L0042-20071011

Observational clinical study: A clinical study in which participants identified as belonging to study groups are assessed for biomedical or health outcomes. Participants may receive diagnostic, therapeutic, or other types of interventions, but the investigator does not assign participants to specific interventions[8].

Official title: The title of the clinical trial, corresponding to the title of the protocol.

Orphadata: A platform developed by Orphanet to provide the scientific community with comprehensive, high-quality and freely accessible datasets related to rare diseases and orphan drugs, in a reusable format.

Orphanet Coordinating Team (OCT): French US14 Inserm-based team coordinating the Orphanet Network, producing the English Orphanet nomenclature and its scientific annotations and responsible for coordination of the production of the scientific content and for all Network activities including translation and IT developments.

Orphanet National Teams (ONT): An Orphanet team based in one of the member countries of the Orphanet Network as per the Orphanet Network Agreement, and responsible for the collection of data on national expert resources. Some of the national teams are also in charge of the translation of the Orphanet nomenclature and/or the Orphanet database.

Orphanet network: Means the ONTs contributing to the Orphanet Database in the frame of the signed Network Agreement and DTAs.

Orphanet online registration service: Service allowing the professionals to register and/or update their activities related to rare diseases in the Orphanet database.

Phase: Clinical drug development is often described as consisting of four phases (Phase I-IV). If the drug successfully passes through phases I, II, and III, it will usually be approved by the national regulatory authority for use in the general population. For more information, please refer to the annex of this document definition of clinical trials phases.

Principle investigator (PI): The person who is responsible for the scientific and technical direction of the entire clinical study[9]. For Orphanet, the PI in the case of a national single site trial is the leading investigator responsible for the conduct of the trial at the site. In national multicentric trials, the PI is the investigator responsible for coordinating the work of the investigators at different sites. In both cases he/she is the investigator who signs the protocol along with the sponsor. In case of a multinational clinical trial, the PI is the national coordinating investigator responsible for coordinating the work of the investigators at the different sites in the country. He/she will have the responsibilities of the sponsor of the study in his/her country and be the national contact person for the study.

[8] https://clinicaltrials.gov/ct2/about-studies/glossary
[9] https://clinicaltrials.gov/ct2/about-studies/glossary

Rare disease (RD): A disease that affects less than 5 in 10,000 persons in Europe, as defined by the European Regulation on orphan medicinal products (Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products). In order to be registered in Orphanet, the disease must be described in at least two independent individuals, confirming that it is not an incidental association of clinical signs.

Sponsor: An individual, company, institution, or organisation that takes responsibility for the initiation, management, and/or financing of a clinical trial[10].

Trial identifying number: Unique ID number assigned by a registry to a trial when registered in that registry.

Type of clinical trial: Clinical trials that are registered in Orphanet database are "labelled" in order to enable the classification of the clinical trials according to their objectives. For more information please refer to the annex of this document: definition of clinical trials types.

6. Filing and updates

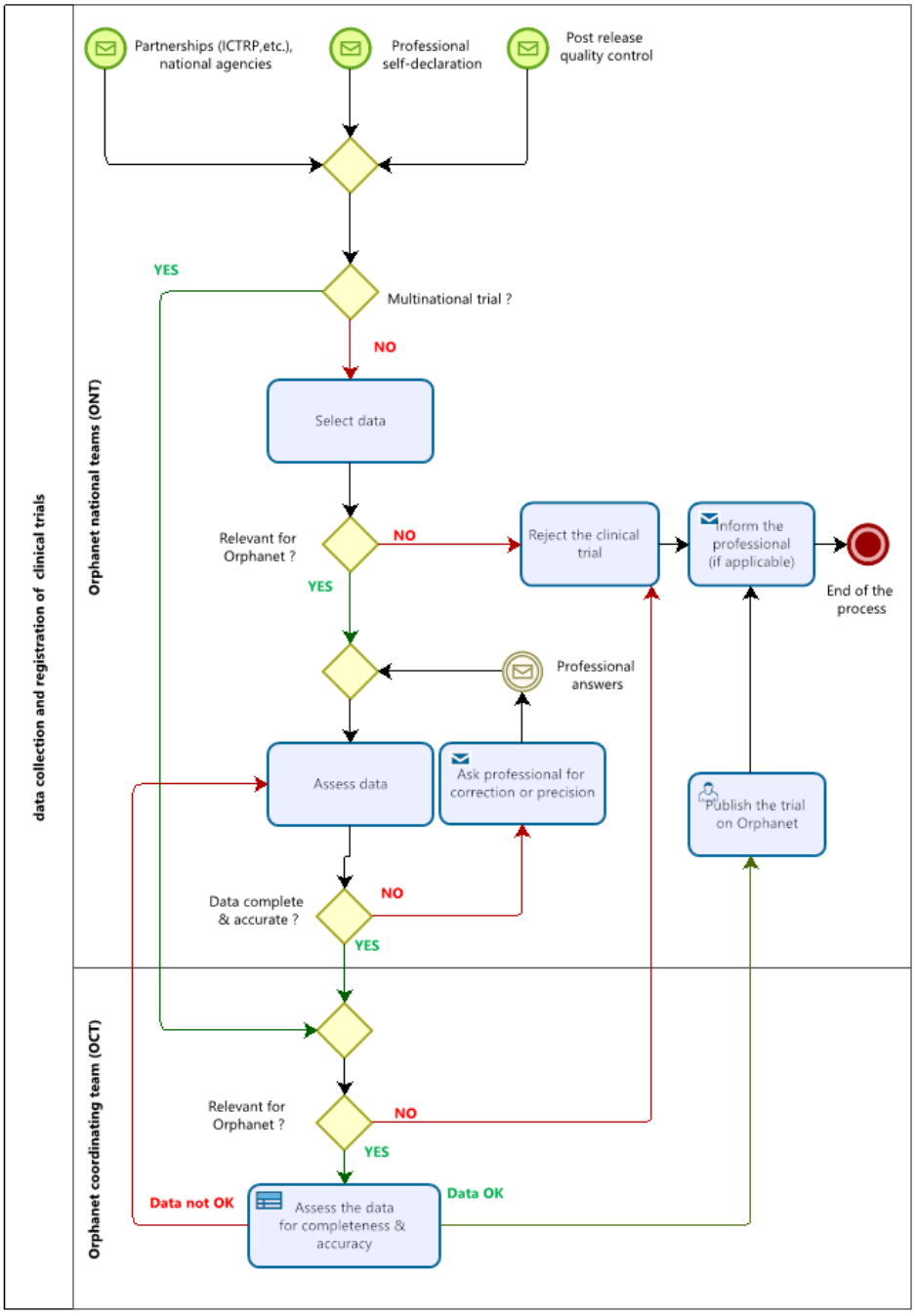
This document is updated by the coordinating team as often as necessary and at least once a year. The most up-to-date version is available on the Orphanet website: https://www.orpha.net/orphacom/cahiers/docs/GB/Clinical_trials_in_Orphanet_R2_R_D_CT_EP_02.pdf

[10] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

II. Methodology

1. Flowchart

The general process for clinical trials data collection, registration, validation and its quality control is presented below:



[11]

[11] Powered by Bizagi Modeler

2. Description

The process of registration/update of national and multinational clinical trials starts with:

- the monthly collection of clinical trials by the Orphanet coordinating team (OCT) through a partnership with the WHO's International Clinical Trial Register Platform (ICTRP).
- an exchange of data through a partnership with a source of data (e.g. national regulatory authorities granting authorisations to conduct clinical trials).
- annual collection of clinical trials funded by IRDiRC members.
- aprofessional requests the registration of its activity through the Orphanet online registration service or in any form (e-mail, phone calls, etc.), or by sending an email request for the update of its registered clinical trials.
- a post-release quality control task focused on national or multinational clinical trials.

An annual update is organised and launched by the OCT. All principal investigators of clinical trials / networks of clinical trials registered in the database are invited to review and update their activities. National teams are responsible for the follow-up of their feedback.

3. Sources of information

National teams are in charge of identifying the sources of information for clinical trials in their countries, and are advised to establish partnerships with them to be as exhaustive as possible.

When establishing a partnership, national teams must inform the coordinating team, as some types of partnerships require the signature of a data transfer agreement (DTA).

The main sources of information are:

- National or international clinical trials database: ICTRP, Clinical trials.gov, EudraCT
- List of clinical trials through a partnership with national authorities
- Clinical trials conducted by health providers members of European Reference Networks (ERN)
- IRDiRC
- Scientific publications
- Professionals declaring a clinical trial through the Orphanet online registration service

4. Data selection

Orphanet national teams (ONT) are responsible of the data selection of national clinical trials that are only performed in their own country and of the one they receive through the Orphanet online registration service.The OCT is in charge of data selection of multinational clinical trials.

The data selection starts by verifying that the clinical trial meets the inclusion criteria for Orphanet

a) Inclusion criteria

In order to be registered in Orphanet, a clinical trial should meet the following inclusion criteria:

- Interventional study
- Specific to a rare disease or a group of rare diseases

- Evaluating a drug, a protocol or a medical device
- Conducted in at least one country of the Orphanet network or funded by an IRDIRC member
- Authorised by national regulatory authorities

b) Exclusion criteria

Orphanet does not register a clinical trial if it is a:

- Observational clinical study (such studies will be registered as research projects).
- Clinical trial on a common disease which has rare forms e.g. Parkinson, breast cancer, etc.
- Clinical trial evaluating an intervention other than drug or medical device (e.g. Surgery, behavioural therapy, etc.)
- Clinical trial conducted outside the Orphanet network unless sponsored / funded by an IRDIRC member.
- Clinical trials non-authorised by national regulatory authorities

5. Data assessment

If the clinical trial complies with the Orphanet inclusion criteria for clinical trials, the information scientist (IS) analyses the information to check that the mandatory dataset (cf. below) is provided and that it is coherent, and eventually introduces the necessary corrections before submitting to pre-release quality control.

In case of inconsistency or missing information, the IS will contact the principal investigator (PI) or contact person of the trial in order to clarify or obtain the information needed.

a) Orphanet dataset for national clinical trials:

i) Mandatory dataset

1) Official title (in local language and in English)
2) Link to the description of the clinical trial protocol, or to a clinical trial database
3) The disease(s) or group of diseases covered by the clinical trial
4) The Drug(s) the trial studies, if relevant
5) Name and contact details (email address and phone number) of the principal investigator (PI),
6) Name and address of the PI's institution where the clinical trial is conducted
7) Name and contact details (email address and phone number) of the sponsor

8) The geographical coverage of the trial: national, European (conducted in EU member states only), global (international)
9) If the trial is sponsored or funded by a member of IRDIRC[12] at the time the study starts
10) The phase of the trial

[12] The IRDiRC status is attributed to a clinical trial when the sponsor and/or funding body is a member of IRDiRC at the time the study started.

11) Type of clinical trial representing the clinical trial's objective
12) EUDRACT number for trials conducted in a European Member State, or other trial identifying number for trials conducted outside the European Union (EU)
13) If the trial is ongoing or terminated
14) If the trial is currently recruiting
15) If the trial is a multicentre trial at national level
16) The start and end dates of the trial

ii) Optional dataset

1) Name and contact details (email address and phone number) of investigators other than the PI involved in the clinical trial
2) Funding body

b) Orphanet dataset for a multinational clinical trial:

The dataset of multinational clinical trials is the same than the dataset of national clinical trials, except for items 13 to 16 that are site-specific and entered for each of the national nodes of the multicentric clinical trial. For clinical trials that are conducted by European Reference Networks, a specific mention is added.

6. Pre-release quality control (PrRQC)

Once the candidate clinical trial passes the assement step, the OCT performs a pre-release quality control to assess the relevance and correctness of data collected by the national teams.
This quality control is mainly focused on the disease(s) linked, the type of clinical trial, the link to the drugs being evaluated, and on the coherence of the whole dataset.

In case some information is missing or needs correction, the form is transfered back to the national teams.

7. Data publication

Once all the quality control steps have been completed, the information on national and multinational clinical trials is accessible on the Orphanet website and can be retrieved from Orphadata after signing a Data Transfer Agreement (DTA) or a service contract.
Once the trial is published on Orphanet website, the corresponding ONT is in charge of informing the professional(s) that the activity has been published.

8. Post-release quality control

The post-release quality control includes one main activity: quality control projects.
Quality control projects: Projects organised by the coordinating team on a regular basis to check the completeness and consistency of the data (e.g. update of the status, completeness of the mandatory dataset, etc.).

III. Annexes

α. Definition of types of clinical trials:

• **Drug clinical trial**: Clinical trial which tests a new substance or group of substances for the treatment of a disease in order to obtain the "marketing authorization" to bring a medicine to the market. It also includes post-marketing (phase IV) trials. A clinical trial evaluating a new substance in association with other established protocols is considered as drug clinical trial.

• **Protocol clinical trial**: Clinical trial which tests alternative protocols for medicines that already meet the standards of safety, quality and efficacy, and are granted a marketing authorisation.

• **Gene therapy clinical trial**: Clinical trial which tests protocols involving the insertion of genes into an individual's cells and/or tissues to treat a disease. Genetically modified cells, where therapeutic effect relates directly to the expression of the genetic sequence, are considered as gene therapy.

• **Cell therapy clinical trial**: Clinical trial which tests the process of introducing new cells into a tissue in order to treat a disease. Cell therapies often focus on the treatment of hereditary diseases. Examples: blood and bone marrow transplantation, tissue repair and regeneration.

• **Vaccine clinical trial**: Clinical trial which tests a treatment that uses a substance or group of substances (inactivated, attenuated compounds from micro-organisms or synthetic peptides, carbohydrates or antigens) to stimulate the immune system to destroy a tumor or infectious microorganisms such as bacteria or viruses.

• **Medical device trial**: Clinical trial which tests a medical device in patients.

β. Definition of clinical trials phases[13]:

Phase I: This phase starts with the initial administration of an investigational new drug into humans, often referred to as "first-in-man studies". Most typical type of study is human pharmacology. Studies in this phase of development usually have non-therapeutic objectives and are conducted in a small group of healthy volunteers or certain types of patients. They are designed for initial safety and tolerability estimation, pharmacokinetics characterisation, assessment of pharmacodynamics, etc...

Phase II: Studies in this phase aim at exploring therapeutic efficacy. Most typical kind of study in phase II, is therapeutic exploratory. They are typically conducted in a group of patients who are selected by relatively narrow criteria, leading to a relatively homogeneous population. An important goal for this phase is to determine the dose and regimen for phase III trials, evaluate potential study endpoints, target population, etc.

Some trials combine Phase I and Phase II, and test both efficacy and safety.

Phase III: Studies in this phase aim at demonstrating or confirming therapeutic benefit. Most typical kind of study in phase III is therapeutic confirmatory. They are designed to confirm the preliminary evidence accumulated in phase II that a drug is safe and effective for use in the intended indication and target population. These trials involve large patient groups and are intended to provide an adequate basis for marketing approval.

Phase IV: Studies in this phase involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives marketing authorization. Phase IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials).

[13] International conference on harmonization (ICH) - Topic E 8 General Considerations for Clinical Trials.

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